

REMARKS

Claims 48, 49, and 93-124 are pending in the present application. Claims 1-46, 50-92, and 125-177 have been cancelled. By virtue of this response, claims 49, 93-97, 101-105, and 114-120 have been amended; and new claims 178-199 have been added. Support for new claim 178 and 179 is found in the specification, *inter alia*, on page 58, lines 18-20. Support for new claims 180-199 are found in the original claims 94 to 113. Accordingly, claims 48, 49, 93-124, and 178-208 are currently under consideration.

With respect to all claim amendments and cancellations, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application.

Telephone Interview

Applicants thank the Examiner Stucker and Examiner Myron G. Hill for extending the courtesy for a telephone interview on February 11, 2004, with Dr. Kim Clary and Applicants' representatives Catherine Polizzi and Jie Zhou, and for providing helpful suggestions, which are reflected in this response. The substance of the interview, during which issues in the Office Action were discussed, is reflected in this response. Claims and art discussed are as indicated in the Interview Summary. All objections and rejections raised in the Office Action were discussed, and the points presented are reflected in this response.

Supplemental Information Disclosure Statement

A supplemental Information Disclosure Statement accompanies this response. Applicants respectfully request the Examiner consider the references and initial the form 1449.

Amendment to the specification

This Amendment is submitted in order to correct the numbering requirement in the PTO-948 in Figures 2, 8, 10, 11, 14, 15, 16, 18, 19, 21, 22, 26, 31, 33, 34, 35, 36, and 37 for the above-referenced application.

Objections to Claims

The Examiner objected claim 49 is objected for misspelled word "lclaim".

Applicants respectfully note that claim 49 is amended to correct the misspelled word. Applicants respectfully request withdrawal of this objection.

Rejections under 35 U.S.C. §112, second paragraph

Claims 47-49 and 93-124 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which application regards as the invention.

A) The Examiner rejects claims 47-49, 93-97, 101-105, 114-124, alleging that "it is not clear what the metes and bounds of 'stress' or 'sub-lethal stress' are and what specific parameters define them."

Applicants respectfully traverse this rejection.

As discussed during the interview, the term "stress" is clearly described in the specification. Page 58, line 21 to page 59, line 30. The specification teaches that "stress can be effectively characterized, and tested, on the basis of the negative effect of the stress condition or stress agent on cellular growth and/or metabolism" and "stress can be achieved by the introduction of any condition or agent that inhibits cellular growth and/or metabolism, or by altering the level of a pre-existing condition or agent such that it becomes sub-optimal with respect to cellular growth and/or metabolism." Page 58, lines 21-25. Thus, the term "stress" is clear to one skilled in the art when the claim is read in light of the specification. The Examiner suggested during the interview to use one term in the claims. The term "sub-lethal" in claims 93-97, 101-105, and 117 is replaced with the term "stress". In view of the above, Applicants respectfully request withdrawal of this rejection.

B) The Examiner rejects claims 47-49, 93-116, alleging "it is not clear what the metes and bounds of 'about' is and what the comparative basis is for the 2 fold and what culture conditions are required."

Applicants respectfully traverse this rejection. As discussed during the interview, Applicants respectfully submit that the term "about" used in claim 47 ("about two-fold") and claim 100 ("elevating the pH to about 8.0") is clear to one skilled in the art. Further, the term "about" is permissible under the law and Office practice. Applicant respectfully submits that the use of the term "about" does not render claims using this term indefinite. It is well established that the use of a relative term does not render a claim indefinite under 35 USC § 112, second paragraph. See Seattle Box Co. v. Industrial Crating & Packaging, Inc., 731 F.2d 818, 221 USPQ 568 (Fed. Cir. 1984) (stating that the fact that the claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite); see also U.S. Patent & Trademark Office, Manual of Patent Examining Procedure § 2173.05(b). Claims are definite where "the claims, read in light of the specification, reasonably apprise those skilled in the art and are as precise as the subject matter permits. As a matter of law, no court can demand more." Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94, 95 (Fed. Cir. 1986). Applicant also notes that the Federal Circuit found the limitation "exceeding about" to be definite in W.L. Gore & Assoc., Inc. v. Garlock, Inc., 721 F.2d 1540, 1557 (Fed. Cir. 1983). Further, a search of the USPTO's web site reveals that the PTO has issued in excess of 22,000 patents between January 1996 and October 1, 2002 with the term "between about" included in the claim language; and 17 patents between January 2000 and March 2004 with the term "about two fold" included in the claim language.

In view of the above, Applicants respectfully request withdrawal of this rejection.

C) The Examiner rejects claims 47-49, 93-98, and 100-116, alleging "it is not clear if this is in cell lysates or in the supernatants of unlysed cells."

Applicants respectfully traverse this rejection. As discussed with the Examiner during the interview, claims are directed to methods of generating a population of rAAV particles by culturing or subjecting cells under a stress condition. Therefore, the rAAV particles may be

generated from the lysed cells, the cell culture medium or both. Applicants respectfully request withdrawal of this rejection.

D) The Examiner rejects claims 47, 93, and 117, alleging that these claims "are incomplete". Examiner states that these claims need a conclusion wherein a population of rAAV particles is generated. The Examiner also states that claims 47 and 93 require at least a step of generating/collecting virus.

Applicants respectfully note that the Examiner indicated during the telephone interview that amending claims to recite that "whereby the rAAV particles are generated" will overcome this rejection. Accordingly, claim 93 and 117 are amended to recite the language. Since claim 47 already recites "whereby about two-fold or more rAAV particles are produced ...", claim 47 is not amended. Applicants respectfully request withdrawal of this rejection.

Rejections under 35 U.S.C. §103(a)

Claims 47-49 and 93-101, 103-113 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Shenk and Bantel-Schaal. With respect to Shenk, the Examiner states that Shenk teaches methods of producing rAAV particles using producer cells having a heterologous DNA flanked by at least one inverted terminal repeat (ITR), helper AAV DNA coding one or more AAV packaging proteins needed for replication and encapsidation, and helper virus (adenovirus). The Examiner further states that Shenk also teaches that AAV helper genes can be linked to a variety of promoters and regulatory sequences including inducible promoters, packaging genes can be stably integrated into the producer cell, and introduction of rAAV vector can be done prior to infection, simultaneously to infection, or after infection. The Examiner also states that "Shenk does not teach culture under stress conditions." With respect to Bantel-Schaal, the Examiner states that Bantel-Schaal teaches conditions in which AAV can be produced in cells and stress can induce AAV production. The Examiner also states that Bantel-Schaal indicates that stress conditions (chemical (toxin), temperature, and radiation (UV)) lead to delay of cell growth retardation. The Examiner also states that DNA replication in cells cultured under stress conditions in the absence of helper virus is known (page 263, col. 1, lines 8-11) and that the stress induces more virus production (Figure 2). The Examiner argues that one of ordinary skill in the art would have been motivated to

use stress conditions to produce more virus as taught by Bantel-Schaal because it would lead to increased rAAV production even in the absence of helper. The Examiner further argues that it would have been *prima facie* obvious to grow rAAV of Shenk under the conditions of Bantel-Schaal to increase viral yield to generate a population of rAAV particles with the expectation of success.

Applicants respectfully traverse this rejection.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three criteria must be met. First, there must be some suggestion, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. These requirements are summarized in the MPEP (MPEP §2143, and §2143.01 to §2143.03), and are based on well-settled case law: *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); and *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

As discussed during the interview, Applicants respectfully submit that the cited references do not provide the motivation to combine reference teachings. As indicated by the Examiner, Shenk does not teach or suggest producing rAAV particles by culturing cells under any stress conditions. Applicants respectfully note that Bantel-Schaal does not teach or suggest production of recombinant AAV by culturing cells under a stress condition in the presence of a helper virus or a helper virus function. As discussed during the telephone interview, Bantel-Schaal discloses stress treatment of cells infected with wild type AAV results in an increase of wild type AAV DNA replication in the absence of helper virus. However, Bantel-Schaal does not teach or suggest that these stress conditions can be used for production of recombinant AAV particles in the presence of a helper virus or a helper virus function. Figure 1C of the reference shows AAV replication is induced in AAV infected cells after they are treated with various stress-inducing agents, and Figure 2 shows stress induces delay of cell growth in AAV-infected cells (unlike what has been pointed out by the Examiner that Figure 2 shows the stress induces virus production). The

Examiner has not provided any basis to support that stress conditions which induce replication of wild type AAV in the absence of helper virus would lead to combination with a reference that teaches general conditions for rAAV production. Accordingly, there is no evidence that one skilled in the art would have been motivated to use stress conditions taught by Bantel-Schaal in rAAV production system of Shenk. Thus, the cited references do not provide the motivation to combine references teachings. The rejection may be properly withdrawn on this ground.

In addition, the Examiner has not provided any evidence to support the argument that it would have been *prima facie* obvious to grow rAAV of Shenk under the conditions of Bantel-Schaal to increase viral yield to generate a population of rAAV particles with the expectation of success. As discussed above, the references cited by the Examiner do not teach or suggest that growing cells stress conditions would increase production of rAAV in the presence of a helper virus or a helper virus function. The Examiner has not provided any basis to support that stress conditions which induce replication of wild type AAV in the absence of helper virus would lead to an increased production of rAAV particles in the presence of a helper virus or a helper virus function. Thus, Applicants respectfully submit there is no reasonable expectation of success. The rejection may be properly withdrawn on this ground.

In view of the above, Applicants respectfully request withdrawal of this rejection.

Double Patenting

A. Claims 47-49 and 93, 94 and 96 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 126 and 159-162 of Allowed U.S. Patent Application No. 09/526,333.

Applicants will address this issue when otherwise allowable subject matter for this application has been identified.

B. Claims 47-49 and 93, 94, 96, 117 and 118 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 118 of co-pending Application No. 10/016,767.

Applicants will address this issue when otherwise allowable subject matter for this application has been identified.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

CONCLUSION

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no.226272003311. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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